IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant-Appellant(s)	Cowley et al.	Examiner:	BRISTOL, LYNN ANNE
Serial No.:	10/511,794	Group Art Unit:	1643
Filed:	March 17, 2005	Docket:	976-20 PCT/US/RCE
Confirmation No:	6673	Dated:	March 9, 2009
For:	SPECIFIC ANTIBODY FRAGMENTS FOR THE HUMAN CARCINOEMBRYONIC ANTIGEN (CEA)		

Board of Patent Appeals and Interferences
United States Patent and Trademark Office
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APPEAL BRIEF PURSUANT TO 37 C.F.R. §41.37

Sir:

This is an appeal to the United States Patent and Trademark Office Board of Patent Appeals and Interferences from a rejection of Claims 32-36, 39-43, and 47-56 in the Office Action mailed October 9, 2008. This Appeal Brief is being submitted under the provisions of 37 C.F.R. § 41.37.

As required by 37 C.F.R. § 41.37(a)(2), please charge Deposit Account No. 082461 the fee of $270.00, as set forth in 37 C.F.R. § 41.20(b)(2), for this Appeal Brief. If additional fees are required or if there are any overpayments, please charge or credit Deposit Account No. 082461 for such sum.

A timely Notice of Appeal was filed on January 9, 2009, thus making this Appeal Brief due March 9, 2009. This Appeal Brief is being filed in support of the Notice of Appeal.

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This Appeal Brief contains these items under the following headings and in the order set forth below:

I. REAL PARTY IN INTEREST

The real party in interest is Centro de Ingenieria Genetica y Biotecnologia, which is the assignee of the entire right, title, and interest in and to the present application.

II. RELATED APPEALS AND INTERFERENCES

There are no prior or pending appeals, interferences, or judicial proceedings known to Appellant or Appellant's legal representative which may be related to, directly affect, or be directly affected by, or have a bearing on, the Board's decision in this present appeal.

III. STATUS OF CLAIMS

Claims 1-31 were filed in the original application. During prosecution of the application, claims 32-56 were added and claims 1-31, 37-38, and 44-46 were canceled.

The subject matter of claims 32-36 and 39-43 were rejected in an Advisory Action dated May 20, 2008 and the subject matter of Claims 47-56 were rejected in an Office Action dated January 4, 2008. Claims 32-36, 39-43, and 47-56 were finally rejected in an Office Action dated October 9, 2008. Accordingly, claims 32-36, 39-43, and 47-56 are presently pending in the application and stand as finally rejected.

The final rejection of claims 32-36, 39-43, and 47-56 is being appealed. No other claims are pending. The claims, as they now stand, are set forth in the Claims

Appendix.

IV. STATUS OF AMENDMENTS

An Office Action was mailed on October 9, 2008, finally rejecting claims 32-36, 39-43, and 47-56. Other than the Notice of Appeal, no amendments or responses were filed subsequent to the mailing of the final rejection of claims.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The following is a concise explanation of the subject matter defined in each of the independent claims involved in the appeal, with reference to the specification by page and line number. Claims 32, 36, 39, 43, 47, 51, 52, and 56 are the independent claims on appeal.

The present invention as set forth in independent claims 32 and 47 are directed to a monomeric single-chain Fv antibody fragment (specification p. 6, lines 8-11). Claims 32 and 47 merely differ in the transition term, *i.e.*, "consisting of" or "comprising," respectively. The monomeric single-chain Fv antibody fragment consists of or comprises an amino acid sequence as set forth in SEQ ID NO: 16 (specification p. 9, lines 29-33; Figure 2; p. 7, lines 13-17). The monomeric single-chain Fv antibody fragment is specific for human carcinoembryonic antigen (specification p. 6, lines 8-11).

The present invention as set forth in independent claims 36 and 51 are directed to a pharmaceutical composition (specification, p. 8, lines 29-34). Claims 36 and 51 merely differ in the transition term, *i.e.*, "consisting of" or "comprising,"

respectively. The pharmaceutical composition consists of or comprises an amino acid sequence as set forth in SEQ ID NO: 16 (specification p. 8, lines 15-18; p. 9, lines 29-33; Figure 2; p. 7, lines 13-17). The pharmaceutical composition further includes a pharmaceutically-acceptable carrier (specification, p. 8, lines 29-34).

The present invention as set forth in independent claims 39 and 52 are directed to a divalent single-chain Fv antibody fragment (specification p. 6, lines 12-16). Claims 39 and 52 merely differ in the transition term, *i.e.*, "consisting of" or "comprising," respectively. The divalent single-chain Fv antibody fragment consists of or comprises an amino acid sequence as set forth in SEQ ID NO: 17 (specification p. 9, lines 29-33; Figure 2; p. 7, lines 13-17). The divalent single-chain Fv antibody fragment is specific for human carcinoembryonic antigen (specification p. 6, lines 12-16).

The present invention as set forth in independent claims 43 and 56 are directed to a pharmaceutical composition (specification, p. 8, lines 29-34). Claims 43 and 56 merely differ in the transition term, *i.e.*, "consisting of" or "comprising," respectively. The pharmaceutical composition consists of or comprises an amino acid sequence as set forth in SEQ ID NO: 17 (specification p. 8, lines 15-18; p. 9, lines 29-33; Figure 2; p. 7, lines 13-17). The pharmaceutical composition further includes a pharmaceutically-acceptable carrier (specification, p. 8, lines 29-34).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The sole rejection to be reviewed on this appeal is:

1. Whether claims 32-36, 39-43, and 47-56 are unpatentable under 35 U.S.C. § 103(a) by Tormo et al. (*APMIS*, 97(12): 1073-80 (1989), Abstract) in view of Freyre et al. (*J. Biotechnol.* 76:157-163 (2000), as evidenced by Ayala et al. (*Conf. on Plant-Made Pharmaceuticals*, 2005), and in further view of Holliger et al. (*PNAS*, 90:6444-48 (1993).

VII. ARGUMENT

I. Rejection under 35 U.S.C. § 103(a) by Tormo, in view of Freyre, as evidenced by Ayala, and in further view of Holliger.

Claims 32-36, 39-43, and 47-56

Tormo discloses a murine monoclonal antibody directed against carcinoembryonic antigen (CEA) in human adult tissues (Tormo, abstract, first sentence). Tormo fails to disclose or suggest, *inter alia*, any single-chain Fv (abbreviated "scFv") antibody fragment and any fragment comprising or consisting of the amino acid sequences as set forth in SEQ ID NOs: 16 or 17.

As explained in the specification on page 6, lines 8-16, and page 3, lines 16-19, a monoclonal antibody differs from scFv antibody fragments in that scFv fragments have a linker sequence connecting the V_H and V_L domains, they lack Fc domains, and they have lower molecular weights than the corresponding monoclonal antibody. These properties facilitate the ability of scFv antibody fragments to penetrate tissues *in vivo* and exhibit reduced immunogenicity. In addition, a monomeric scFv antibody fragment differs from a diabody scFv antibody fragment in structure and molecular size (specification, page 4, lines 8-12 and 17-19).

The examiner acknowledges that Tormo fails to disclose or suggest, *inter alia*, any single-chain Fv antibody fragment. The examiner applies Freyre for its disclosure of an scFv antibody fragment that was produced using a murine monoclonal antibody directed against CEA. (See page 4, second to third paragraphs, of the October 9, 2008

office action).

Freyre discloses scFv antibody fragments that were developed by using RNA extracted from hybridoma cells that produce the murine monoclonal antibody against CEA (see paragraph bridging pp. 157-8 of Freyre).

Ayala (2005) teaches that the scFv antibody fragments disclosed in Freyre exhibited a reduced affinity for the target CEA antigen when compared to the antigen affinity exhibited by the Fab fragment of the parent monoclonal antibody. Contrary to the examiner's assertions, Ayala (2005) does not identify or predict that the reduced antigen affinity exhibited by the scFv of Freyre was due to PCR mutations. Ayala discloses the creation of another scFv antibody fragment in which measures were taken to avoid potential introduction of PCR mutations. However, Ayala does not identify or predict any reason for the reduced affinity for CEA observed in Freyre. As is appreciated in the art, many various and unpredictable factors may contribute to an observation of low antigen affinity.

Holliger discloses a method to clone V_H and V_L domains from a parent monoclonal antibody into an scFv antibody fragment.

The cited references, alone or in combination, fail to disclose or suggest any amino acid sequence, much less the specific amino acid sequences as required by claims 32-36, 39-43, and 47-56. In fact, the examiner provided no evidence establishing that any of the cited references taught or suggested any amino acid sequence even remotely related to the claimed sequences.

The examiner has acknowledged that the same combination of cited references is devoid of, *inter alia*, any disclosure of the claimed amino acid sequences. For example, the examiner did not reject original claims 2 and 4 on pages 16-19 of the June 7, 2007 office action. Original claims 2 and 4 were directed to single-chain Fv antibody fragments comprising amino acid sequences encoded by SEQ ID NO: 16 or 17, respectively. Claims 2 and 4 were canceled merely in order to address claim objections, and were rewritten as claims 32 and 39 in the amendment of October 5, 2007.

Moreover, none of the cited references in combination or individually disclose or suggest any compositions that are structurally similar to the recited compositions in the instant claims, which concern scFv antibody fragments having specific amino acid sequences. For example, the claimed monomeric and divalent scFv antibody fragments have important differences in the amino acid sequences of the V_H and V_L domains when compared with prior art scFv fragments. See specification p. 3, lines 29-35. There are differences with at least sixteen amino acids in the V_H domains and with at least three amino acids in the V_L domains between the claimed scFv fragments and those disclosed in Ayala et al. (*Biotechniques* 13: 790-799, 1992). *Id.* Ayala (1992) was cited in the Freyre reference on page 158: "...we have developed several scFv gene constructions that have been expressed as biologically active antibody fragments in the periplasm of *Escherichia coli* (Ayala et al., 1992)").

In addition, as stated above, monoclonal antibodies and scFv antibody fragments are constructed differently, and they differ structurally and functionally. For

example, scFv antibody fragments differ from a monoclonal antibody in that scFv fragments have a linker sequence connecting the V_H and V_L domains, they lack Fc domains, and they have lower molecular weights than the corresponding monoclonal antibody. Accordingly, contrary to the examiner's assertion on page 4 of the October 9, 2008 office action, the claimed scFv antibody fragments are not "inherent" based on the disclosure of the monoclonal antibody in Tormo, and they are not structurally similar to the compositions disclosed in the references.

"To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'" *In re Robertson*, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted).

Here, the claimed monovalent and diabody scFv antibody fragments are not necessarily present in the monoclonal antibody described in Tormo. The mere fact that the scFv antibody fragments may result from the monoclonal antibody of Tormo is insufficient, especially given the structural differences between scFv fragments and monoclonal antibodies. The examiner's inherency assertion also fails when viewed in light of the imperfect scFv antibody fragments of the prior art (e.g., Freyre (2000) and Ayala (1992)), which exhibited low CEA affinity and were created using RNA from hybridoma cells that produced monoclonal antibodies against CEA. Accordingly, the examiner failed to establish a rejection of the claims based on inherency.

It is well settled that, to support an obviousness rejection, "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970).

Appellant respectfully submits that the pending obviousness rejection made by the examiner is in error because the examiner failed to take into consideration all of the elements of the pending claims. The examiner failed to consider the specific amino acid sequence elements of the pending claims, and the examiner failed to consider the structural differences between the claimed scFv antibody fragments and the compositions disclosed in the references. Accordingly, the examiner failed to establish a *prima facie* case of obviousness and the claims should be passed to allowance.

The United States Supreme Court addressed the standard for obviousness in its decision of *KSR International Co. v. Teleflex, Inc. et al.*, 550 U.S. 389; 127 S.Ct 1727; 82 U.S.P.Q.2d 1385 (2007) and the importance of predictability. In its decision, the Supreme Court stated that "If a person of ordinary skill can implement a predictable variation, §103 likely bars its patentability." 82 U.S.P.Q.2d at 1396. The Supreme Court further stated that:

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

Id. at 1397.

In the present application, the examiner asserted that a reasonable expectation of success existed in producing the claimed antibody fragments because:

> ...all of the materials and reagents were available for producing the recombinant CEA Abs, and...the importance of V_H and V_L sequence fidelity in generating a scFv with high affinity binding was established...and Hollinger [*sic.*] provided an alternative method to for [*sic.*] cloning V_H and V_L domains from a parent Mab into a scFv or diabody structure...

See page 4, fourth paragraph of the October 9, 2008 office action.

Contrary to the examiner's assertions, however, merely having "all the materials and reagents...available for producing the recombinant CEA Abs" was not sufficient for any predictability or reasonable expectation of success for arriving at the claimed scFv antibody fragments.

At the time of the invention, indeed, one skilled in the art knew how to produce an scFv antibody fragment derived from the murine monoclonal antibody against CEA. See, for example, Freyre (2000) at page 158 ("starting with RNA from ior-cea.1 hybridoma cells, we have developed several scFv gene constructions that have been expressed as biologically active antibody fragments..."), and the specification at page 2, lines 29-31, citing Ayala, *Biotechniques*, 13: 790-799 (1992), for disclosing the development of an scFv antibody fragment obtained by PCR of the RNA extracted from the hybridoma producing a monoclonal antibody against CEA.

However, scFv antibody fragments developed by previous investigators (*e.g.*,

Freyre (2000) and Ayala (1992)), failed to exhibit a high affinity for the target antigen CEA and a proper biodistribution in test animals. See specification at p. 2, lines 29-40, and Ayala (2005), first paragraph, which states that the affinity of the scFv disclosed in Freyre "was shown to be 200 times lower than that of the Fab obtained by enzyme digestion of the original Mab" (citations omitted). Accordingly, at the time of the invention, there was "a design need or market pressure to solve a problem" regarding low affinity for CEA by the scFv antibody fragments previously constructed.

Nothing in the combined cited references disclosed, taught, or suggested that there was any "finite number of identified, predictable solutions" to the problem. For example, nothing in the cited references identified or predicted any causes or reasons for the observed low CEA affinity. Contrary to the examiner's assertion and reliance upon Ayala (2005), the importance of V_H and V_L sequence fidelity in generating a scFv antibody fragment with high affinity binding was not established in the references at the time of the invention. As Appellant explained earlier, Ayala (2005) discloses the creation of a scFv antibody fragment in which measures were taken to avoid potential introduction of PCR mutations. However, Ayala does not state that the reduced antigen affinity exhibited by the scFv of Freyre was due to PCR mutations. In fact, Ayala does not disclose or suggest any reason for the reduced affinity for CEA observed in Freyre.

Nothing in the cited references identified or predicted what specific mutations, if any, were allegedly present in the scFv fragments disclosed therein. For example, the combined cited references are devoid of any identification or prediction of the at

least sixteen amino acid differences in the V_H domains and the at least three amino acids in the V_L domains between the claimed scFv fragments and those of the prior art. See specification p. 3, lines 29-35. That is, nothing in the combination of cited references identified or predicted any sequence variations to make for correcting any alleged PCR mutations in order to arrive at the claimed invention. In fact, as explained above, the combination of cited references lacked any disclosure of any amino acid sequences for scFv fragments.

A person of ordinary skill at the time of the invention, therefore, did not have "a finite number of identified, predictable solutions" nor any "known options within his or her technical grasp" to pursue in order to address the problem of scFv antibody fragments having a low affinity for CEA. Merely having "all the materials and reagents...available for producing the recombinant CEA Abs" did not provide any sufficient degree of predictability or reasonable expectation of success.

Appellant respectfully submits that there was no reasonable expectation of success for arriving at the claimed invention. Accordingly, a *prima facie* case of obviousness has not been established and the claims should be passed to allowance.

Conclusion

For the foregoing reasons, the invention of claims 32-36, 39-43, and 47-56 are patentably distinct from the combination of references cited in the Office Action of October 9, 2008. Appellant respectfully requests reversal of the rejections of claims 32-36, 39-43, and 47-56.

Respectfully submitted,

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VIII. CLAIMS APPENDIX

The claims involved in the Appeal are:

32. A monomeric single-chain Fv (scFv) antibody fragment consisting of an amino acid sequence as set forth in SEQ ID NO: 16, wherein the monomeric scFv antibody fragment is specific for human carcinoembryonic antigen.

33. An antibody fragment according to claim 32, further comprising a detectable agent.

34. An antibody fragment according to claim 33, wherein the detectable agent is a radioactive label.

35. An antibody fragment according to claim 33, wherein the detectable agent is a reporter molecule.

36. A pharmaceutical composition consisting of an amino acid sequence as set forth in SEQ ID NO: 16 and a pharmaceutically-acceptable carrier.

39. A divalent single-chain Fv (scFv) antibody fragment consisting of an amino acid sequence as set forth in SEQ ID NO: 17, wherein the divalent scFv antibody fragment is specific for human carcinoembryonic antigen.

40. An antibody fragment according to claim 38, further comprising a detectable agent.

41. An antibody fragment according to claim 39, wherein the detectable agent is a radioactive label.

42. An antibody fragment according to claim 39, wherein the detectable agent is a reporter molecule.

43. A pharmaceutical composition comprising an amino acid sequence as set forth in SEQ ID NO: 17 and a pharmaceutically-acceptable carrier.

47. A monomeric single-chain Fv (scFv) antibody fragment comprising an amino acid sequence as set forth in SEQ ID NO: 16, wherein the monomeric scFv antibody fragment is specific for human carcinoembryonic antigen.

48. An antibody fragment according to claim 47, further comprising a detectable agent.

49. An antibody fragment according to claim 48, wherein the detectable agent is a radioactive label.

50. An antibody fragment according to claim 48, wherein the detectable agent is a reporter molecule.

51. A pharmaceutical composition comprising an amino acid sequence as set forth in SEQ ID NO: 16 and a pharmaceutically-acceptable carrier.

52. A divalent single-chain Fv (scFv) antibody fragment comprising an amino acid sequence as set forth in SEQ ID NO: 17, wherein the divalent scFv antibody fragment is specific for human carcinoembryonic antigen.

53. An antibody fragment according to claim 52, further comprising a detectable agent.

54. An antibody fragment according to claim 53, wherein the detectable agent is a radioactive label.

55. An antibody fragment according to claim 53, wherein the detectable agent is a reporter molecule.

56. A pharmaceutical composition comprising an amino acid sequence as set forth in SEQ ID NO: 17 and a pharmaceutically-acceptable carrier.

IX. EVIDENCE APPENDIX

None.

X. RELATED PROCEEDINGS APPENDIX

None.